

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 19672-002WO1	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2006/039682	International filing date (day/month/year) 11/10/2006	(Earliest) Priority Date (day/month/year) 14/10/2005
Applicant CHUGAI SEIYAKU KABUSHIKI KAISHA		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. 1
☒ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
b. ☐ none of the figures is to be published with the abstract

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International application No.

PCT/US2006/039682

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
 - a. type of material
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☒ on paper
 - ☒ in electronic form
 - c. time of filing/furnishing
 - ☒ contained in the international application as filed
 - ☒ filed together with the international application in electronic form
 - ☐ furnished subsequently to this Authority for the purpose of search
2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

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International application No

PCT/US2006/039682

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K39/395 C07K16/18 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 1 411 118 A1 (ABURATANI HIROYUKI [JP]; CHUGAI PHARMACEUTICAL CO LTD [JP]) 21 April 2004 (2004-04-21) paragraph [0010] paragraph [0021] paragraph [0068] - paragraph [0071]	1-11
Y	WO 2005/023301 A (ABURATANI HIROYUKI [JP]; CHUGAI PHARMACEUTICAL CO LTD [JP]; PERSEUS PR) 17 March 2005 (2005-03-17) the whole document -/--	1-11



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

2 April 2007

Date of mailing of the international search report

13/04/2007

Name and mailing address of the ISA/

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Authorized officer

Irion, Andrea

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2006/039682

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	& EP 1 671 645 A (CHUGAI PHARMACEUTICAL CO LTD [JP]; PERSEUS PROTEOMICS INC [JP]; ABURAT) 21 June 2006 (2006-06-21) paragraph [0010] paragraph [0011] paragraph [0018] paragraph [0072] - paragraph [0075] paragraph [0059] -----	1-11
Y	WO 2004/099249 A (XENCOR [US]; LAZAR GREGORY ALAN [US]; CHIRINO ARTHUR J [US]; DANG WEI) 18 November 2004 (2004-11-18) paragraph [0024] - paragraph [0031] the whole document -----	1-11
P,Y	WO 2006/006693 A (CHUGAI PHARMACEUTICAL CO LTD [JP]; NAKANO KIYOTAKA [JP]; YOSHINO TAKES) 19 January 2006 (2006-01-19) the whole document	1-11
P,Y	& EP 1 674 111 A (CHUGAI PHARMACEUTICAL CO LTD [JP]) 28 June 2006 (2006-06-28) the whole document -----	1-11
P,Y	WO 2006/022407 A (CHUGAI PHARMACEUTICAL CO LTD [JP]; KINOSHITA YASUKO [JP]; SUGIMOTO MAS) 2 March 2006 (2006-03-02) the whole document -----	1-11
P,Y	WO 2006/046751 A (CHUGAI PHARMACEUTICAL CO LTD [JP]; NAKANO KIYOTAKA [JP]; SUGO IZUMI [J]) 4 May 2006 (2006-05-04) paragraph [0064] -----	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/039682

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 7 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/039682

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 1411118	A1	21-04-2004	CA 2451493 A1 CN 1688692 A WO 03000883 A1 US 2004236080 A1	03-01-2003 26-10-2005 03-01-2003 25-11-2004
WO 2005023301	A	17-03-2005	EP 1671645 A1	21-06-2006
EP 1671645	A	21-06-2006	WO 2005023301 A1	17-03-2005
WO 2004099249	A	18-11-2004	AU 2004236160 A1 BR PI0410031 A CA 2524399 A1 EP 1620467 A2 KR 20050116400 A	18-11-2004 25-04-2006 18-11-2004 01-02-2006 12-12-2005
WO 2006006693	A	19-01-2006	AU 2005256113 A1 BR PI0506125 A CA 2544692 A1 CN 1842540 A EP 1674111 A1 MX PA06002890 A	30-03-2006 24-10-2006 19-01-2006 04-10-2006 28-06-2006 05-06-2006
EP 1674111	A	28-06-2006	AU 2005256113 A1 BR PI0506125 A CA 2544692 A1 CN 1842540 A WO 2006006693 A1 MX PA06002890 A	30-03-2006 24-10-2006 19-01-2006 04-10-2006 19-01-2006 05-06-2006
WO 2006022407	A	02-03-2006	NONE	
WO 2006046751	A	04-05-2006	NONE	

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION

See paragraph 2 below

International application No.
PCT/US2006/039682

International filing date (day/month/year)
11.10.2006

Priority date (day/month/year)
14.10.2005

International Patent Classification (IPC) or both national classification and IPC
INV. A61K39/395 C07K16/18 A61P35/00

Applicant

CHUGAI SEIYAKU KABUSHIKI KAISHA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Irion, Andrea

Telephone No. +49 89 2399-8174



Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ on paper
 - ☒ in electronic form
 - c. time of filing/furnishing:
 - ☒ contained in the international application as filed.
 - ☒ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 7 (IA)

because:

☒ the said international application, or the said claims Nos. 7 (IA) relate to the following subject matter which does not require an international search (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13~~ter~~.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2006/039682

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-11</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-11</u>
Industrial applicability (IA)	Yes: Claims	<u>1-6,8-11</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Item III

III.1 With respect to claim 7

Claim 7 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(I) PCT).

Item V

V.1 Reference is made to following documents

- D1: EP1411118 (H. ABURATANI & CHUGAI SEIYAKU KABUSHIKI KAISHA) 21 April 2004 (2004-04-21)
- D2: WO2005023301 (CHUGAI SEIYAKU KABUSHIKI KAISHA & PERSEUS PROTEOMICS INC. & H. ABURATANI) 17 March 2005 (2005-03-17)
- D3: WO2004099249 (XENCOR) 18 November 2004 (2004-11-18)
- D4: WO2006006693 (CHUGAI SEIYAKU KABUSHIKI KAISHA) 19 January 2006 (2006-01-19)
- D5: WO2006022407 (CHUGAI SEIYAKU KABUSHIKI KAISHA) 02 March 2006 (2006-03-02)
- D6: WO2006046751 (CHUGAI SEIYAKU KABUSHIKI KAISHA) 04 May 2006 (2006-05-04)

V.2 Novelty (Article 33(2) PCT)

V.2.1 With respect to claims 1-11

None of the documents cited above describe anti-glypican-3 antibodies having amino acid substitutions within the Fc region. Therefore, the subject-matter of claims 1-11 is considered novel in the sense of Article 33(2) PCT.

V.3 Inventive step (Article 33(3) PCT)

V.3.1 With respect to claims 1-11

Document D1 describes anti-glypican antibodies showing cell proliferation inhibiting activity by ADCC activity and CDC activity (paragraph [0009]). Said antibodies inhibit the growth of cancer cells, e.g. hepatic cancer cells (paragraph [0010], [0021], [0068]-

[0071]). The antibodies may be monoclonal and humanized.

Document D2 describes anti-glypican-3 antibodies having a cytotoxic activity such as antibody-dependent-cytotoxic activity (ADCC) used for the treatment of cholangiocarcinoma (abstract, paragraph [0010], [0011], [0018], [0072]-[0075]). For enhancing the cytotoxic activity of the anti-glypican-3 antibodies, the sugar chain of the antibody may be modified (paragraph [0059]).

Document D3 describes optimized Fc variants and methods for their generation. Antibodies comprising said Fc variants with amino acid substitutions within the Fc region have an enhanced ADCC activity. The amino acid positions substituted are S239D, S298A, A330L, I332E, K326T (paragraph [024]-[031]).

The combinations S239D/A330L/I332E, S239D/A330Y/I332E/K326T S239D/S298A/I332E (paragraph [024], [027]) are disclosed. Said amino acid substitutions are described to result in an enhanced ADCC activity.

The subject-matter of claims 1-11 differs from the closest prior art document D2 in that the anti-glypican-3 antibodies are modified by amino acid substitutions within the Fc region resulting in antibodies showing an enhanced ADCC activity instead of modifying the sugar chain of the antibody as described in D2. The technical problem to be solved may be regarded as providing alternative anti-glypican antibodies. The skilled person is aware of the effect of improving the ADCC activity by substituting the specific amino acid positions as described in D3. Therefore, the skilled person facing the technical problem posed would combine the method described in D3 with the anti-glypican antibodies known from D2 thereby arriving at the subject-matter of claims 1-11. Moreover, the substituted Fc regions referred to as SEQ ID NO. 34-38 are known from D3 (SEQ ID NO. 30, 214, 217, 95). Thus, the subject-matter of claims 1-11 is not considered inventive in the sense of Article 33(3) PCT.

V.4 Industrial applicability (Article 33(4) PCT)

V.4.1 With respect to claims 1-6 and 8-11

The subject-matter of claims 1-6 and 8-11 appears to be susceptible of industrial application.

V.4.2 With respect to claim 7

The subject-matter of claim 7 is considered to be a method of treatment by therapy of the human or animal body

For the assessment of the present claim 7 on the question whether they are

industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Item VI

VI.1 With respect to documents D4-D6

The examination report has been based on an assumed valid priority for the present application. Should the priority of the present application not be valid, the above cited documents D4-D6 would be relevant with respect to novelty and inventive step (Article 33(2) and (3) PCT). Furthermore, should the present application be entered into the regional phase, the document D4-D6 could be relevant to the question of novelty.